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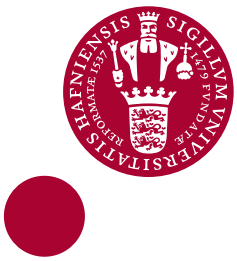

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RESEARCH ARTICLE

Sacubitril/valsartan reduces serum uric acid concentration, an independent predictor of adverse outcomes in PARADIGM-HF

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Aims Elevated serum uric acid concentration (SUA) has been associated with an increased risk of cardiovascular disease, but this may be due to unmeasured confounders. We examined the association between SUA and outcomes as well as the effect of sacubitril/valsartan on SUA in patients with heart failure with reduced ejection fraction (HFrEF) in PARADIGM-HF.

Methods and results The association between SUA and the primary composite outcome of cardiovascular death or heart failure (HF) hospitalization, its components, and all-cause mortality was examined using Cox regression analyses among 8213 patients using quintiles (Q1–Q5) of SUA adjusted for baseline prognostic variables including estimated glomerular filtration rate (eGFR), diuretic dose, and log N-terminal pro-brain natriuretic peptide. Change in SUA from baseline over 12 months was also evaluated in each treatment group. Patients in Q5 (SUA ≥8.6 mg/dL) compared with Q1 (<5.4 mg/dL) were younger (62.8 vs. 64.2 years), more often male (88.7% vs. 63.1%), had lower systolic blood pressure (119 vs. 123 mmHg), lower eGFR (57.4 vs. 76.6 mL/min/1.73 m^2), and greater diuretic use. Higher SUA was associated with a higher risk of the primary outcome (adjusted hazard ratios) Q5 vs. Q1 = 1.28 [95% confidence intervals (1.09–1.50), $P = 0.003$], cardiovascular death [1.44 (1.11–1.77), $P = 0.001$], HF hospitalization [1.37 (1.11–1.70), $P = 0.004$], and all-cause mortality [1.36 (1.13–1.64), $P = 0.001$]. Compared with enalapril, sacubitril/valsartan reduced SUA by 0.24 (0.17–0.32) mg/dL over 12 months ($P < 0.0001$). Sacubitril/valsartan improved outcomes, irrespective of SUA concentration.

Conclusion Serum uric acid concentration was an independent predictor of worse outcomes after multivariable adjustment in patients with HFrEF. Compared with enalapril, sacubitril/valsartan reduced SUA and improved outcomes irrespective of SUA.

Keywords Heart failure • Uric acid • Mortality • Neprilysin • Angiotensin

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[†]A complete list of the PARADIGM-HF investigators can be found in the supplementary material online, *Appendix S1*.

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Introduction

Uric acid (UA) is the final product of purine metabolism and the serum concentration of UA (SUA) reflects the balance between dietary intake of purines, the synthesis of UA by xanthine oxidase (along with superoxide) and UA excretion, principally by the kidneys but also through the gastrointestinal tract.[1,2] Diuretic treatment is also associated with high SUA, probably because diuretics impair UA excretion.

As well as potentially reflecting oxidative stress as a consequence of xanthine oxidase activity,[1] UA may itself have harmful effects such as increasing expression of cytokines and chemokines, inducing inflammation, impairing endothelial function and activating the renin–angiotensin system.[2]

Hyperuricemia is common in many forms of cardiovascular disease, including heart failure (HF).[3] In patients with acute and chronic HF, higher SUA is associated with worse clinical outcomes.[4,5] Whether SUA is an independent predictor of outcome is less certain as renal function and use of diuretics (and diuretic dose) has been variably adjusted for. Additionally, only one prior study has adjusted for natriuretic peptide levels and that was a study in acute HF.[6]

The effect of treatments for HF on UA concentration is also of interest and UA lowering agents have been investigated as a potential therapy for HF.[7,8] We have, therefore, examined the predictive value of SUA in the Prospective comparison of ARNI with ACEI to Determine Impact on Global Mortality and morbidity in Heart Failure trial (PARADIGM-HF)[9] and determined the effect of sacubitril/valsartan (formerly known as LCZ696) on SUA.

Methods

Patients and procedures

The design and primary results of PARADIGM-HF have been reported previously.[9–11] Briefly, PARADIGM-HF was a randomized, double-blinded comparison of the ARNI sacubitril/valsartan with enalapril in patients with chronic HF with reduced ejection fraction (HFrEF). Eligibility criteria at screening included New York Heart Association (NYHA) classes II–IV, left ventricular ejection fraction (LVEF) $\leq$ 40% (changed to $\leq$35% by amendment), and elevated natriuretic peptides. Exclusion criteria at screening included symptomatic hypotension or systolic blood pressure $<$ 100 mmHg, estimated glomerular filtration rate (eGFR) $<$30 mL/min/1.73 m^2, and potassium $>$5.2 mmol/L.

On trial entry, ongoing therapy with angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) was stopped and patients entered sequential run-in, first receiving enalapril 10 mg b.i.d. for 2 weeks followed by sacubitril/valsartan for additional 4–6 weeks up titrated from 100 mg to 200 mg b.i.d. Patients tolerating both drugs at these target doses were randomly assigned to double-blinded therapy with sacubitril/valsartan or enalapril in a 1:1 ratio.

Measurement of SUA was performed at screening, during run-in (when changing from enalapril to sacubitril/valsartan), at randomization, and after 2, 4, and 12 months of follow-up and yearly thereafter. Evaluations of SUA were performed through a central laboratory. SUA was converted from μmol/L to mg/dL by division with 59.48. The upper limit of normal for the SUA assay used was 8.0 mg/dL for men and 7.3 mg/dL for women aged 66–90 years, and 6.9 mg/dL for women aged 18–65 years.

Outcomes

The primary endpoint in PARADIGM-HF was a composite of cardiovascular death and HF hospitalization. In this study, we investigated the association between SUA and the risk of the primary outcome, each of its components, and all-cause mortality. All endpoints were adjudicated by a clinical endpoint committee in a blinded fashion. We also compared the effects of the randomized treatment on SUA 4, 12, and 24 months after randomization, as described below.

Statistical analyses

Baseline characteristics are presented as frequencies and percentages for categorical variables and means with standard deviation or medians with interquartile range for continuous variables. Differences in baseline characteristics were tested using χ^2 test for categorical variables and analysis of variance (ANOVA) or Kruskal–Wallis test for continuous variables. Use of loop diuretics at baseline was grouped in categories of furosemide equivalents: 40 mg furosemide = 20 mg torasemide = 1 mg bumetanide. Non-loop diuretics (primarily thiazide and indapamide) were categorized as 'other'.

Incidence rates for each outcome of interest are presented per 100 person years of follow-up. Event rates in each SUA quintile were estimated by the Kaplan–Meier method and compared using the log-rank test. Cox proportional hazards regression models were used to compare hazard ratios (HRs) with 95% confidence intervals (CIs) according to SUA quintiles. In multivariable models, the HR was adjusted for the following baseline characteristics: age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, NYHA class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, eGFR, haemoglobin, sodium, albumin, randomized treatment (sacubitril/valsartan), diuretic dose, and log transformed N-terminal pro brain natriuretic peptide (NT-proBNP).

The association between SUA and each outcome was also assessed in an adjusted model using a restricted cubic spline with five knots using SUA of 7.0 mg/dL as reference.[3]

For the risk of each of the outcomes, there were no interactions between SUA levels and sex. The proportional hazards assumption was evaluated using plots of Schoenfeld residuals vs. log time and found valid, as was the assumption of linearity of continuous variables.

Changes in SUA were assessed by repeated measures mixed model with the baseline score as a covariate, and treatment, region, time, and treatment by time interaction as fixed effects, with a common unstructured covariance for each treatment group.

Analyses were performed using Stata version 13 (Stata Corp., College Station, TX, USA) and SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All *P*-values are two-sided, and a *P*-value $<$0.05 was considered significant.

Results

Of the 8399 patients randomized, 8213 had a SUA measurement at randomization. Mean SUA was 6.9 $\pm$ 2.0 mg/dL, 7.1 $\pm$ 2.0 mg/dL in men and 6.1 $\pm$ 1.8 mg/dL in women ($P < 0.001$) (distributions of SUA overall and according to sex and region are illustrated in the supplementary material online, *Figures S1* and *S2*).

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Table 1 Baseline characteristics

	Serum uric acid concentration at randomization					
	Q1 (*n* = 1635)	Q2 (*n* = 1696)	Q3 (*n* = 1688)	Q4 (*n* = 1643)	Q5 (*n* = 1551)	*P*-value
Serum uric acid (mg/dL), mean ± SD	4.4 ± 0.7	5.8 ± 0.3	6.7 ± 0.3	7.9 ± 0.4	9.2 ± 1.2	
mg/dL, range	0.3–5.3	5.4–6.2	6.3–7.2	7.3–8.5	8.6–17.1	
Age at screening (years)	64.16 ± 11.19	64.00 ± 10.98	64.21 ± 11.25	63.61 ± 11.65	62.83 ± 11.84	0.003
Female sex	603 (36.9%)	427 (25.2%)	338 (20.0%)	250 (15.2%)	176 (11.3%)	<0.001
Randomized to sacubitril/valsartan	802 (49.1%)	849 (50.1%)	825 (48.9%)	831 (50.6%)	785 (50.6%)	0.77
Region						<0.001
North America	92 (5.6%)	98 (5.8%)	128 (7.6%)	129 (7.9%)	141 (9.1%)	
Latin America	342 (20.9%)	302 (17.8%)	276 (16.4%)	280 (17.0%)	211 (13.6%)	
Western Europe	282 (17.2%)	360 (21.2%)	432 (25.6%)	427 (26.0%)	484 (31.2%)	
Central Europe	640 (39.1%)	617 (36.4%)	579 (34.3%)	496 (30.2%)	419 (27.0%)	
Asia/Pacific and other	279 (17.1%)	319 (18.8%)	273 (16.2%)	311 (18.9%)	296 (19.1%)	
Race						<0.001
White	1080 (66.1%)	1102 (65.0%)	1148 (68.0%)	1064 (64.8%)	999 (64.4%)	
Black	70 (4.3%)	76 (4.5%)	82 (4.9%)	92 (5.6%)	102 (6.6%)	
Asia	272 (16.6%)	324 (19.1%)	280 (16.6%)	317 (19.3%)	308 (19.9%)	
Other	213 (13.0%)	194 (11.4%)	178 (10.5%)	170 (10.3%)	142 (9.2%)	
Systolic blood pressure (mmHg)	123.38 ± 15.04	123.03 ± 15.79	121.10 ± 15.43	120.40 ± 14.73	118.55 ± 14.94	<0.001
Heart rate (b.p.m.)	72.13 ± 11.28	72.05 ± 11.79	71.81 ± 12.07	72.56 ± 12.22	73.45 ± 12.79	0.001
eGFR 60 mL/min/1.73 m^2	76.61 ± 21.67	71.82 ± 19.08	67.81 ± 18.10	64.22 ± 18.17	57.38 ± 18.05	<0.001
Serum creatinine (μmol/L)	84.95 ± 21.88	92.27 ± 22.34	98.06 ± 22.96	104.79 ± 24.22	117.83 ± 28.20	<0.001
Ischaemic HF aetiology	1007 (61.6%)	1001 (59.0%)	1021 (60.5%)	983 (59.8%)	900 (58.0%)	0.291
Ejection fraction (%)	29.98 ± 6.03	29.93 ± 6.06	29.57 ± 6.17	29.22 ± 6.33	28.63 ± 6.37	<0.001
Body mass index (kg/m^2)	27.31 ± 5.16	27.61 ± 5.44	28.14 ± 5.34	28.67 ± 5.73	29.15 ± 5.79	<0.001
Current smoking	225 (13.8%)	264 (15.6%)	234 (13.9%)	226 (13.8%)	232 (15.0%)	0.440
NYHA class						0.001
I	66 (4.0%)	82 (4.8%)	76 (4.5%)	82 (5.0%)	77 (5.0%)	
II	1164 (71.2%)	1209 (71.3%)	1210 (71.7%)	1191 (72.5%)	1016 (65.5%)	
III	391 (23.9%)	390 (23.0%)	388 (23.0%)	363 (22.1%)	436 (28.1%)	
IV	13 (0.8%)	14 (0.8%)	10 (0.6%)	6 (0.4%)	16 (1.0%)	
Unknown	1 (0.1%)	1 (0.1%)	4 (0.2%)	1 (0.1%)	6 (0.4%)	
Duration of HF						<0.001
≤1 year	553 (33.8%)	537 (31.7%)	503 (29.8%)	468 (28.5%)	417 (26.9%)	
1–5 years	597 (36.5%)	682 (40.2%)	644 (38.2%)	644 (39.2%)	605 (39.0%)	
>5 years	485 (29.7%)	477 (28.1%)	541 (32.0%)	531 (32.3%)	529 (34.1%)	
A history of						
Hypertension	1152 (70.5%)	1216 (71.7%)	1191 (70.6%)	1158 (70.5%)	1084 (69.9%)	0.847
Diabetes	555 (33.9%)	570 (33.6%)	577 (34.2%)	562 (34.2%)	579 (37.3%)	0.171
Myocardial infarction	704 (43.1%)	689 (40.6%)	761 (45.1%)	718 (43.7%)	666 (42.9%)	0.126
Valvular heart disease	98 (6.0%)	116 (6.8%)	128 (7.6%)	114 (6.9%)	136 (8.8%)	0.038
Atrial fibrillation	507 (31.0%)	551 (32.5%)	608 (36.0%)	661 (40.2%)	688 (44.4%)	<0.001
HF hospitalization	958 (58.6%)	1009 (59.5%)	1055 (62.5%)	1060 (64.5%)	1080 (69.6%)	<0.001
Stroke	138 (8.4%)	132 (7.8%)	138 (8.2%)	148 (9.0%)	152 (9.8%)	0.282
COPD	182 (11.1%)	202 (11.9%)	213 (12.6%)	239 (14.5%)	218 (14.1%)	0.018
Cancer	83 (5.1%)	81 (4.8%)	80 (4.7%)	85 (5.2%)	72 (4.6%)	0.946
Medications						
Beta-blocker	1516 (92.7%)	1578 (93.0%)	1571 (93.1%)	1537 (93.5%)	1439 (92.8%)	0.898
Mineralocorticoid receptor antagonist	849 (51.9%)	889 (52.4%)	947 (56.1%)	967 (58.9%)	926 (59.7%)	<0.001
Digoxin	409 (25.0%)	493 (29.1%)	496 (29.4%)	549 (33.4%)	543 (35.0%)	<0.001
Diuretics						<0.001
None	465 (28.4%)	407 (24.0%)	347 (20.6%)	262 (15.9%)	159 (10.3%)	
Loop diuretic – furosemide <40 mg	450 (27.5%)	492 (29.0%)	495 (29.3%)	459 (27.9%)	355 (22.9%)	
Loop diuretic – furosemide 40–80 mg	449 (27.5%)	482 (28.4%)	528 (31.3%)	537 (32.7%)	551 (35.5%)	
Loop diuretic – furosemide >80 mg	174 (10.6%)	215 (12.7%)	231 (13.7%)	296 (18.0%)	437 (28.2%)	
Other	97 (5.9%)	100 (5.9%)	87 (5.2%)	89 (5.4%)	49 (3.2%)	

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Table 1 Continued

	Serum uric acid concentration at randomization					
	Q1 (*n* = 1635)	Q2 (*n* = 1696)	Q3 (*n* = 1688)	Q4 (*n* = 1643)	Q5 (*n* = 1551)	*P*-value
Uric acid lowering drugs						0.082
None	1440 (88.1%)	1521 (89.7%)	1525 (90.3%)	1471 (89.5%)	1411 (91.0%)	
Allopurinol	188 (11.5%)	167 (9.8%)	159 (9.4%)	169 (10.3%)	134 (8.6%)	
Febuxostat	5 (0.3%)	6 (0.4%)	0 (0.0%)	1 (0.1%)	2 (0.1%)	
Benzbromarone	2 (0.1%)	2 (0.1%)	4 (0.2%)	1 (0.1%)	4 (0.3%)	
Sulfinpyrazone	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.1%)	0 (0.0%)	
Laboratory values at randomization						
Haemoglobin (g/L)	137.31 ± 15.20	138.84 ± 15.66	139.86 ± 15.48	140.71 ± 16.42	140.06 ± 17.09	<0.001
Albumin (g/L)	42.71 ± 3.08	42.71 ± 3.09	42.80 ± 3.14	42.76 ± 3.16	42.93 ± 3.29	0.249
Sodium (mmol/L)	141.34 ± 3.14	141.67 ± 3.02	141.45 ± 2.97	141.38 ± 2.96	141.43 ± 3.06	0.084
Any ICD (including CRT-D) use	197 (12.0%)	214 (12.6%)	250 (14.8%)	273 (16.6%)	283 (18.2%)	<0.001
CRT	90 (5.5%)	104 (6.1%)	117 (6.9%)	120 (7.3%)	132 (8.5%)	0.010
BNP (pg/mL)	231 (147.0–413.3)	241.2 (145.3–420.7)	248.4 (150.9–452.9)	253.7 (157.5–478.4)	310.2 (171.8–631.7)	<0.001
NT-proBNP (pg/mL)	1374 (792–2715)	1527.5 (862–2730)	1548.0 (840–3105)	1669.5 (941–3249)	2132.0 (1104–4707)	<0.001
KCCQ clinical summary score	81.3 (62.5–92.7)	81.3 (65.0–92.7)	81.3 (64.1–92.2)	79.2 (63.5–91.7)	77.1 (60.2–90.1)	<0.001

Data are numbers (proportion), mean ± standard deviation, and median (interquartile range), as appropriate.
BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; HF, heart failure; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; Q, quintile.

Table 2 Risk of various endpoints according to uric acid levels at randomization

	No. events	Crude rate per 100 PY	Unadjusted HR (95% CI)	*P*-value	Adjusted HR[a] (95% CI)	*P*-value
Primary composite						
Q1: <5.4 mg/dL	320	9.3 (8.3–10.4)	1.00 (reference)		1.00 (reference)	
Q2: 5.4–6.2 mg/dL	352	9.8 (8.8–10.9)	1.05 (0.91–1.23)	0.49	1.00 (0.85–1.16)	0.97
Q3: 6.3–7.2 mg/dL	382	10.8 (9.8–12)	1.17 (1.01–1.35)	0.042	1.03 (0.88–1.20)	0.71
Q4: 7.3–8.5 mg/dL	415	12.5 (11.3–13.8)	1.34 (1.16–1.55)	<0.001	1.07 (0.92–1.25)	0.37
Q5: ≥8.6 mg/dL	518	17.9 (16.4–19.5)	1.91 (1.66–2.19)	<0.001	1.28 (1.09–1.50)	0.003
CV death						
Q1: <5.4 mg/dL	191	5.2 (4.5–6)	1.00 (reference)		1.00 (reference)	
Q2: 5.4–6.2 mg/dL	229	6.0 (5.3–6.9)	1.15 (0.95–1.4)	0.14	1.11 (0.91–1.35)	0.29
Q3: 6.3–7.2 mg/dL	226	6.0 (5.2–6.8)	1.14 (0.94–1.39)	0.18	1.04 (0.85–1.27)	0.70
Q4: 7.3–8.5 mg/dL	252	7.0 (6.2–7.9)	1.34 (1.11–1.62)	0.002	1.17 (0.96–1.43)	0.12
Q5: ≥8.6 mg/dL	330	10.2 (9.1–11.4)	1.96 (1.64–2.34)	<0.001	1.44 (1.17–1.77)	0.001
HF hospitalization						
Q1: <5.4 mg/dL	167	4.8 (4.2–5.6)	1.00 (reference)		1.00 (reference)	
Q2: 5.4–6.2 mg/dL	191	5.3 (4.6–6.1)	1.10 (0.89–1.35)	0.38	1.02 (0.83–1.26)	0.84
Q3: 6.3–7.2 mg/dL	229	6.5 (5.7–7.4)	1.34 (1.10–1.64)	0.004	1.14 (0.93–1.40)	0.21
Q4: 7.3–8.5 mg/dL	252	7.6 (6.7–8.6)	1.56 (1.28–1.90)	<0.001	1.17 (0.95–1.44)	0.14
Q5: ≥8.6 mg/dL	325	11.2 (10.1–12.5)	2.28 (1.89–2.75)	<0.001	1.37 (1.11–1.70)	0.004
All-cause mortality						
Q1: <5.4 mg/dL	246	6.7 (5.9–7.6)	1.00 (reference)		1.00 (reference)	
Q2: 5.4–6.2 mg/dL	282	7.4 (6.6–8.4)	1.10 (0.93–1.31)	0.26	1.07 (0.89–1.27)	0.48
Q3: 6.3–7.2 mg/dL	283	7.5 (6.7–8.4)	1.11 (0.94–1.32)	0.23	1.02 (0.85–1.21)	0.86
Q4: 7.3–8.5 mg/dL	312	8.7 (7.7–9.7)	1.29 (1.09–1.52)	0.003	1.13 (0.95–1.35)	0.18
Q5: ≥8.6 mg/dL	395	12.2 (11.1–13.5)	1.82 (1.55–2.14)	<0.001	1.36 (1.13–1.64)	0.001

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; PY, person years; Q, quintile.
[a]Adjusted for the following baseline-variables: age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, New York Heart Association class, history of HF hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, estimated glomerular filtration rate, haemoglobin, sodium, albumin, randomized treatment (sacubitril/valsartan), diuretic dose, and log N-terminal pro-brain natriuretic peptide.

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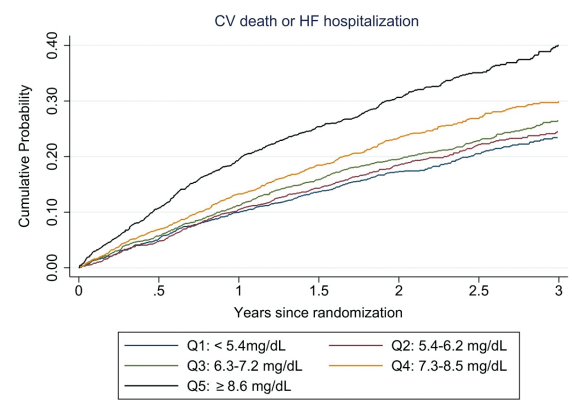

Figure 1 Cumulative probability of the primary endpoint according to quintile (Q) of uric acid concentration at randomization. CV, cardiovascular; HF, heart failure.

Serum uric acid and baseline characteristics

Patient characteristics according to quintile (Q1–Q5) of SUA are shown in *Table 1*. There were many differences between patients with higher and lower SUA. Patients with higher SUA were slightly younger and much more likely to be male. North American and Western European patients were over-represented among those with higher SUA, as were patients of Asian and Black race. Although some differences were small, the patients with higher SUA had an overall profile suggesting more advanced HF. Specifically, duration of HF was longer, NYHA class and KCCQ were worse and a history of prior HF hospitalization was more common. LVEF, systolic blood pressure and eGFR were lower and heart rate and NT-proBNP were higher. Of interest, most co-morbidities were not substantially more common in patients with a higher SUA, except for atrial fibrillation (Q5 vs. Q1, 44.4% vs. 31.0%). Diuretic treatment was more frequent in patients with higher SUA (Q5 vs. Q1, 89.9% vs. 71.6%) and diuretic dose was also larger in those with higher SUA. Mineralocorticoid receptor antagonists were also used more often in patients with a higher SUA.

Serum uric acid and clinical outcomes

The rates of the clinical outcomes of interest according to baseline SUA quintile are shown in *Table 2* and *Figure 1*. These are shown in relation to SUA displayed as a continuous variable in *Figure 2*. The primary composite outcome and both its components occurred more frequently in patients with higher UA concentrations although, after adjustment for other prognostic variables (including NT-proBNP, diuretic dose and eGFR) the increase in risk was only clearly seen in those with the highest levels (Q5, 8.6–17.1 mg/dL) using Q1 as reference. Spline analysis suggested a linear increase in risk above a serum concentration of around 7 mg/dL (*Figure 2*). Results were similar when including use of SUA lowering drugs at baseline in the multivariable model (supplementary material online, *Table S1*).

Effect of sacubitril/valsartan on outcomes according to serum uric acid level

The benefit of sacubitril/valsartan over enalapril was consistent across SUA quintiles for all outcomes of interest (*Table 3*; supplementary material online, *Figure S3*).

Effect of sacubitril/valsartan on serum uric acid level

During the run-in period, SUA decreased when switching from enalapril to sacubitril/valsartan and remained lower in the sacubitril/valsartan group than in the enalapril group at 4, 12, and 24 months after randomization (*Figures 3–4* and *Table 4*). At 4 months after randomization, SUA was approximately 0.25 mg/dL (95% CI −0.33, −0.18) lower in the sacubitril/valsartan group and this difference persisted at 12 and 24 months.

Use of serum uric acid lowering agents before and after randomization

Very few patients (approximately 10%) were treated with a UA lowering agent at baseline and use did not vary according to SUA. UA lowering agents were initiated among 301 (7.3%) patients randomized to enalapril, as compared with 244 (6.0%) among those assigned to sacubitril/valsartan (between group $P = 0.015$).

Discussion

Although there are a number of reports of an association between high SUA and poor clinical outcomes in HF, it has not been clear whether UA is independently predictive when taking account of renal function and diuretic therapy, both of which increase UA and are themselves important markers of worse prognosis. More importantly, no prior report in patients with chronic HF included adjustment for natriuretic peptides, which are the single most powerful predictor of outcomes in HF.[6] Our study addresses these gaps in the evidence to date. We found that even after accounting for these other variables, SUA remained a predictor of both death and HF hospitalization, although this was only apparent at concentrations above approximately 7 mg/dL and thus was most apparent in patients in the highest SUA quintile. Notably, we observed this relationship between SUA and outcomes in patients extensively treated with beta-blockers and mineralocorticoid receptor antagonists, in addition to full-dose renin–angiotensin system blockade (in most prior studies patients had not been treated with these contemporary therapies). PARADIGM-HF included patients with less severe HF than in prior reports on the role of SUA, and PARADIGM-HF was also a much more geographically representative cohort.[10,11]

The precise nature of the link between SUA and prognosis in HF has been uncertain. One possibility is that high SUA is an epiphenomenon and just a marker of reduced excretion due to renal impairment or higher diuretic dose. However, our data suggest there may be additional potential mechanisms as SUA remained a predictor of outcome after correcting for those variables. High

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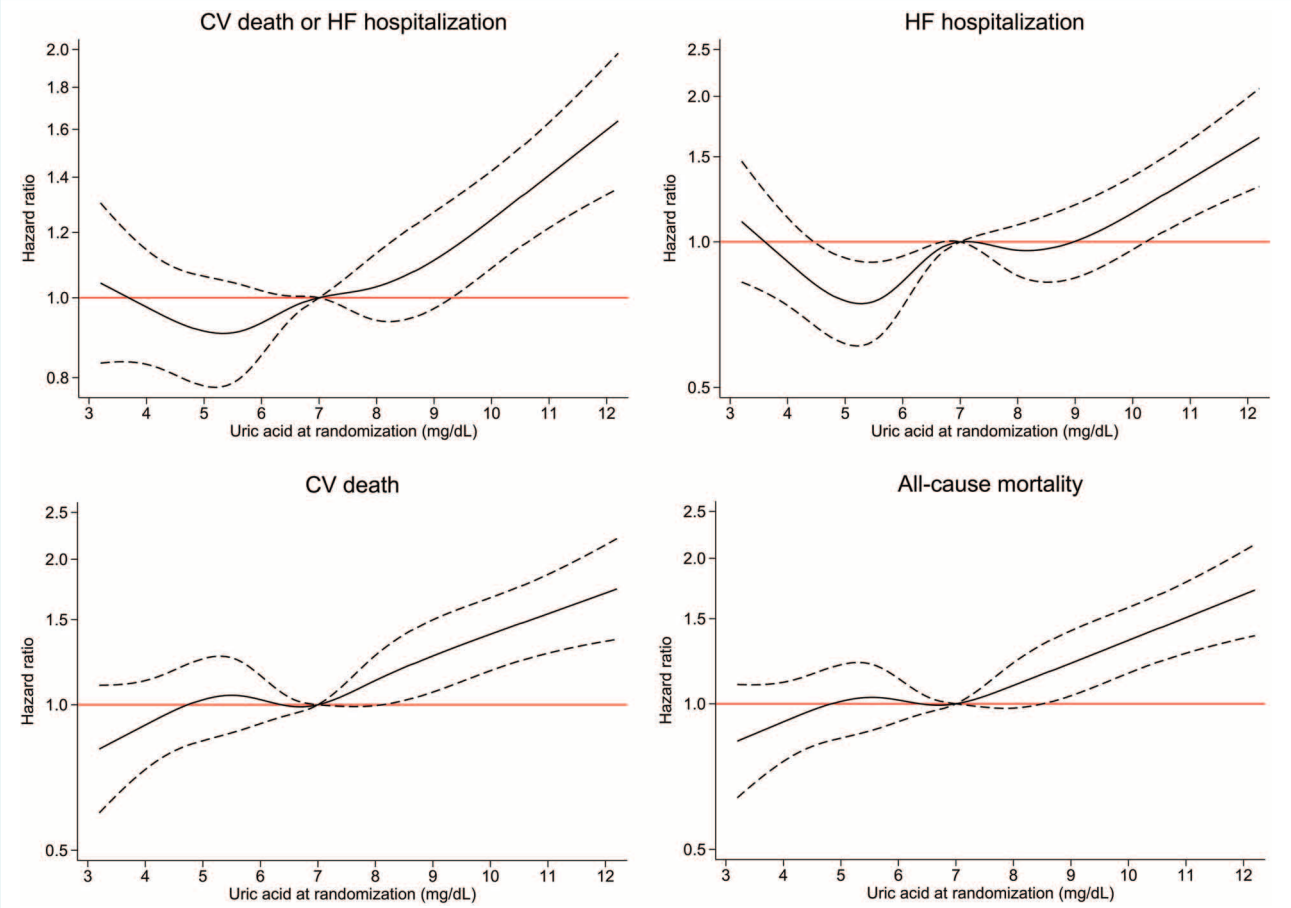

Figure 2 Associations between serum uric acid level at randomization and outcomes. Adjusted for the following baseline variables: age, sex, race, region, systolic blood pressure, heart rate, ejection fraction, New York Heart Association class, history of heart failure (HF) hospitalization, duration of HF, atrial fibrillation, diabetes, body mass index, prior myocardial infarction, prior stroke, estimated glomerular filtration rate, haemoglobin, sodium, albumin, randomized treatment (sacubitril/valsartan), diuretic dose, and log N-terminal pro-brain natriuretic peptide. The reference is 7.0 mg/dL. CV, cardiovascular.

Table 3 Effects of sacubitril/valsartan vs. enalapril on outcomes according to uric acid quintile at randomization

	Q1	Q2	Q3	Q4	Q5	*P*-value for interaction
Primary composite	0.75 (0.60–0.83)	0.80 (0.65–0.99)	0.73 (0.59–0.89)	0.88 (0.73–1.07)	0.81 (0.61–0.96)	0.70
CV death	0.73 (0.55–0.98)	0.82 (0.63–1.06)	0.74 (0.57–0.97)	0.91 (0.71–1.16)	0.76 (0.61–0.95)	0.72
HF hospitalization	0.74 (0.54–1.00)	0.80 (0.60–1.07)	0.76 (0.59–0.99)	0.82 (0.64–1.05)	0.83 (0.67–1.03)	0.98
All-cause mortality	0.80 (0.62–1.03)	0.83 (0.66–1.05)	0.85 (0.67–1.07)	0.93 (0.75–1.16)	0.78 (0.64–0.95)	0.80

CV, cardiovascular; HF, heart failure; Q, quintile.

SUA could also reflect increased xanthine oxidase activity and this, in turn, might result in oxidative stress which is thought to play a detrimental role in HF.[1] It has also been suggested that UA itself has direct effects likely to be harmful in HF.[12] For example, UA may have pro-inflammatory and proliferative actions and cause endothelial dysfunction.[2] Likewise, UA may be damaging in the kidneys.[13] While both possibilities are supported by experimental studies and mechanistic studies in humans, two small randomized clinical studies using xanthine oxidase inhibitors (which lowered SUA levels) have not shown clear clinical benefit in patients with HF.[7,8]

In the Impact of Oxypurinol in Patients With Symptomatic Heart Failure (OPT-HF) study including 405 patients with HFrEF, oxypurinol reduced SUA by ~2 mg/dL at 24 weeks without any clinical benefit overall, although *post hoc* analyses suggested possible benefits in patients with SUA > 9.5 mg/dL (approximating to Q5 in the present analysis).[7] However, in the Effects of Xanthine

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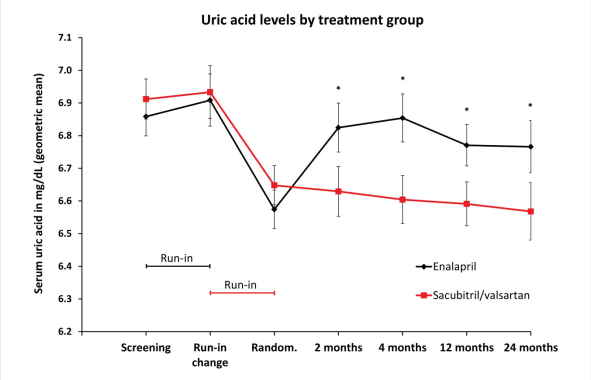

Figure 3 Effect of study drug on serum uric acid concentration. *$P < 0.001$ for sacubitril/valsartan vs. placebo in a repeated measures mixed model, with baseline score as a covariate, and treatment, region, time, and treatment by time interaction as fixed effects. During the first run-in all patients received enalapril but changed to sacubitril/valsartan during the second run-in, as illustrated below the curves.

Oxidase Inhibition in Hyperuricemic Heart Failure Patients (EXACT-HF) study, which included 253 patients with HFrEF and SUA ≥ 9.5 mg/dL, although allopurinol treatment reduced SUA by ~4.2 mg/dL at 24 weeks, it did not improve clinical status, health-related quality of life or LVEF.[8] Because of their limited size, neither of these studies definitively answers the question of whether lowering SUA improves clinical outcomes in HF.

In PARADIGM-HF, treatment with sacubitril/valsartan reduced SUA and did lead to better clinical outcomes. The reduction in SUA of approximately 0.25 mg/dL with sacubitril/valsartan was much smaller than in the studies mentioned above and the reduction was not of a magnitude one would expect to have a substantial effect on clinical outcomes. Whether (and by how much) this reduction in SUA contributed to the reduction in morbidity and mortality observed in PARADIGM-HF is unknown, given the many other beneficial mechanisms of action of sacubitril/valsartan. However, the possibility that lowering SUA might indeed be of value in HF cannot be excluded based on these findings.

The mechanism of the effect of sacubitril/valsartan on SUA is unknown. While losartan is known to have an uricosuric action, this is not the case for other ARBs, including valsartan.[14,15] Inhibition of neprilysin may have such an effect as MDL 100,240, a dual neprilysin-ACE inhibitor, increased urinary UA excretion in a small ($n = 12$) study in human volunteers.[16] We also found a significantly lower use of UA lowering agents after randomization in the sacubitril/valsartan compared with the enalapril group, which may be an additional clinical benefit of angiotensin receptor neprilysin inhibition.

SUA levels may also reflect oxidative stress and SUA itself may increase expression of cytokines and chemokines. Unfortunately, we did not evaluate these pathways in PARADIGM-HF to see whether the effect of sacubitril/valsartan on SUA was accompanied by changes in markers of inflammation.

The question remains as to whether SUA is a marker rather than a mediator of outcomes and our findings of an association between SUA and outcomes do not necessarily reflect cause and effect.[17]

Our study has other limitations. Not all patients had SUA measured at every time point during follow-up. Patients with an eGFR <30 mL/min/1.73 m^2 at screening, during the run-in period or at randomization were excluded, as were patients who experienced a decrease in eGFR >25% (amended to >35%) between screening and randomization. While measurement of SUA was pre-planned, not all of these analyses were. Finally, urinary UA was not measured.

In conclusion, SUA was an independent predictor of worse outcomes in PARADIGM-HF, even after multivariable adjustment. Compared with enalapril, sacubitril/valsartan reduced SUA and improved outcomes irrespective of SUA.

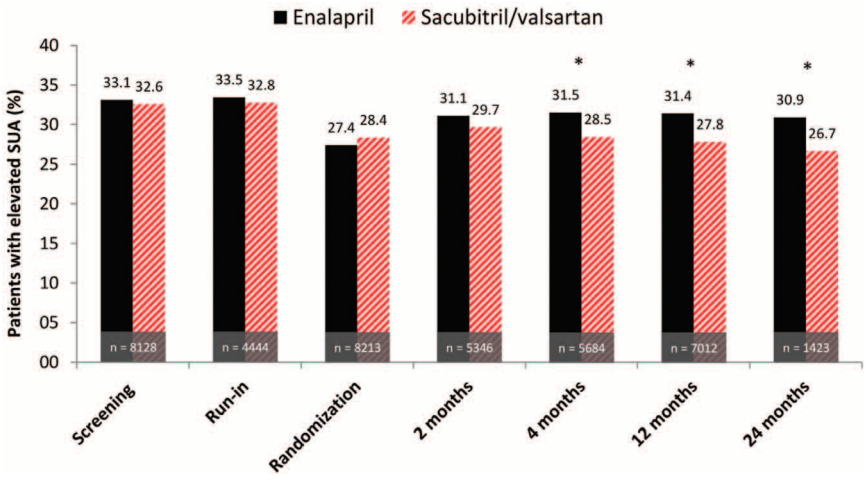

Figure 4 Point prevalence of serum uric acid (SUA) according to randomized treatment *$P < 0.001$. Grey bars illustrate number of patients with measurements at each time point.

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Table 4 Change in uric acid levels at different time points from randomization and from screening

	Sacubitril/valsartan		Enalapril		
	n	LSM (SE)	*n*	LSM (SE)	LSM of difference (95% CI)
Change from randomization (mg/dL) at					
2 months	2592	0.00 (0.025)	2574	0.23 (0.025)**	−0.23 (−0.16, 0.30)**
4 months	2846	−0.01 (0.026)	2838	0.25 (0.026)**	−0.26 (−0.33, 0.18)**
12 months	3529	0.01 (0.025)	3483	0.26 (0.025)**	−0.24 (−0.32, 0.17)**
24 months	2521	0.01 (0.032)	2428	0.29 (0.032)**	−0.28 (−0.37, 0.19)**
Change from screening (mg/dL) at					
0 months (randomization)	4052	−0.26 (0.021)**	4076	−0.30 (0.021)**	0.04 (−0.01, 0.10)
2 months after randomization	2607	−0.27 (0.027)**	2593	−0.05 (0.027)*	−0.21 (−0.29, 0.14)**
4 months after randomization	2869	−0.26 (0.027)**	2856	−0.03 (0.027)	−0.23 (−0.31, 0.16)**
12 months after randomization	3572	−0.25 (0.026)**	3521	−0.02 (0.026)	−0.23 (−0.30, 0.15)**
24 months after randomization	2558	−0.25 (0.032)**	2464	0.01 (0.033)	−0.26 (−0.35, 0.17)**

Data are least square means (LSM) with standard errors (SE) based on a repeated measures mixed model—with the baseline score as a covariate, and treatment, time, and treatment by time interaction as fixed effects.
CI, confidence interval.
*$P < 0.05$, **$P < 0.0001$.

Supplementary Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PARADIGM-HF Investigators.

Figure S1. Distribution of serum uric acid concentrations at randomization.

Figure S2. Distribution of serum uric acid concentrations at randomization according to sex and region.

Figure S3. Hazard ratio of sacubitril/valsartan compared with enalapril for the risk of the primary endpoint according to uric acid level at randomization (green line).

Table S1. Risk of various endpoints according to uric acid levels (SUA) at randomization in a model including use of SUA lowering drugs.

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